An Open Label Trial of Growth Hormone in Children and Adolescents With Phelan-McDermid Syndrome Targeting Social Withdrawal
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Initial Application
IRB-18-01272
Swathi Sethuram

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1. Summary - Title

Protocol Title

An Open Label Trial of Growth Hormone in Children and Adolescents with Phelan-McDermid Syndrome Targeting Social Withdrawal

Principal Investigator	Swathi Sethuram
Primary Department	Pediatrics
Application Initiated By	Swathi Sethuram

Lay Summary

BACKGROUND: Phelan-McDermid syndrome (PMS) is a genetic form of autism spectrum disorder (ASD) associated with developmental delay and hypotonia. IGF-1 promotes brain vessel growth, neurogenesis, and synaptogenesis. Our previous clinical trial of IGF-1 in patients with Phelan McDermid Syndrome has shown improvement in core ASD symptoms using the Aberrant Behavior Checklist (ABC) and the Repetitive Behavior Scale-Revised (RBS-R). Growth hormone (GH) binds to its receptor and initiates a cascade of events which directly increases synthesis and release of IGF-1 levels.

HYPOTHESIS: We hypothesize that rise in IGF-1 stimulated by growth hormone (GH) administration should produce the same improvement in behavior in children and adolescents with Phelan McDermid Syndrome as previously demonstrated with use of IGF-1.

RESEARCH PLAN: We seek to recruit 20 patients with Phelan McDermid Syndrome and administer growth hormone as once daily subcutaneous injections for 12 weeks at standard doses. We will monitor baseline anthropometric measures, laboratory parameters for growth, IGF-1 levels, bone age prior to therapy and continue to monitor safety laboratory parameters during and after therapy. The goal of therapy would be to maintain IGF-1 levels between 1-2SD above the mean for age and puberty. Evaluations of their social withdrawal shall be made using standardized and validated behavioral scales. VEPs will be used as biomarkers of visual sensory reactivity. Each patient will have thorough history and physical evaluations prior to, during and following the trial.

SIGNIFICANCE: Autism is a severe lifelong neuro-developmental disorder. Our pilot trial of IGF-1 in patients with Phelan McDermid Syndrome demonstrated the improvement in their behavioral skills. Growth hormone is an easily accessible medication that has been studied for decades in children with short stature. Its safety profile is well known and administration in children is easier with once daily injections compared to twice daily injections with IGF-1. Also, hypoglycemia which is a serious adverse effect of IGF-1 therapy is not associated with growth hormone therapy. We expect growth hormone to produce similar effects to IGF-1 in these patients considering GH acts via the IGF-1 pathway. This project could perhaps make a breakthrough for treating children with all forms of autism in the future and must be explored.

IF Number IF2355548

2. Summary - Setup

Funding Has Been Requested / Obtained	Yes
Application Type	Request to Rely on Mount Sinai IRB
Research Involves	Prospective Study ONLY
Consenting Participants	Yes
Requesting Waiver or Alteration of Informed Consent for Any Procedures	No
Humanitarian Use Device (HUD) Used Exclusively in the Course of Medical Practice	No
Use of an Investigational Device to Evaluate Its Safety or Effectiveness	No
Banking Specimens for Future Research	No
Cancer Related Research that Requires Approval from the Protocol Review and Monitoring Committee (PRMC).	No

Is this Cancer Related Research? Cancer Related Research is defined as research that has cancer endpoints or has a cancer population as part of or all of its targeted population. This includes protocols studying patients with cancer or those at risk for cancer.

Clinical Trial Yes

**** A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).***
**** Used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.***

Drugs / Biologics Yes

**** Drugs / Biologics That Are Not a Part of Standard Practice***
**** Controlled Substances***
**** Drugs / Biologics Supplied by the Research Sponsor or Purchased with Study Funds***

Ionizing Radiation for imaging or therapy, including X-Ray, Fluoroscopy, CT, Nuclear Medicine, PET andor Radiation Therapy:

*** Purely for standard of care:**	Yes
*** In frequency or intensity that exceeds what is necessary for standard of care:**	Yes

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Hazardous Materials No

**** Recombinant DNA***

**** Viral Vectors***
**** Plasmids***
**** Bacterial Artificial Chromosomes***
**** Toxic Chemicals, Potentially Toxic Medications, Carcinogens***
**** Autologous Cell Lines***

Request Use of Clinical Research Unit Resources No

3. Summary - Background

Objectives

1. To evaluate if growth hormone will adequately elevate IGF-1 levels within 12 weeks of therapy.
Hypothesis: Growth hormone will cause a rise in IGF-1 levels within 12 weeks of therapy.

2. To evaluate efficacy of growth hormone induced elevation in IGF1 on social withdrawal as the primary outcome measure using the ABC – Social Withdrawal subscale (Aman et al., 1985).
Hypothesis: Growth hormone will produce the same effects in improvement in social withdrawal as compared to IGF-1.

3. To evaluate efficacy of Growth hormone induced elevation in IGF1 on repetitive behaviors using the Repetitive Behavior Scale-Revised (Bodfish), sensory reactivity using the Short Sensory Profile (Dunn) and the Sensory Assessment for Neurodevelopmental Disorders (Siper et al., 2017), and hyperactivity using the ABC-Hyperactivity subscale.
Hypothesis: Growth hormone will be associated with improvement across all outcomes comparable with the use of IGF-1.

4. To evaluate the effect of growth hormone therapy on visual evoked potentials and auditory event related potentials in children with Phelan McDermid Syndrome.
Hypothesis: Growth hormone will be associated with similar changes in visual evoked potentials and auditory event related potentials following 12 weeks trial as compared to IGF-1.

Background

In recent years there have been major changes in the understanding of the etiology of autism spectrum disorders (ASD) and many genes associated with ASD have been identified. This has led to a profound shift in thinking, such that ASD can now be conceived of as having multiple independent causes, which in many cases can be largely attributed to a specific etiological genetic event. One such example is the 22q13 deletion syndrome, also called Phelan-McDermid syndrome (PMS), characterized by global developmental delay, hypotonia, delayed or absent speech, and ASD features, for which convincing evidence implicates SHANK3 as the critical gene (Bonaglia et al, 2006). SHANK3 codes for a master scaffolding protein which forms the framework in glutamatergic synapses (Boeckers et al, 2006) and makes up the core of the postsynaptic density (PSD). Recent studies exploring the rate of 22q13 deletions/SHANK3 mutations suggest that haploinsufficiency of SHANK3 can cause a monogenic form of ASD and intellectual disability with a frequency of up to 2% of ASD cases (Durand et al, 2007; Moessner et al, 2007; Gauthier et al, 2008; LeBlond et al., 2015). Although SHANK3 mutations and deletions account for a relatively small proportion of ASD cases, recent evidence suggests that this variant may be treatable, and therefore important to identify.

Work on PMS at our Center began with Shank3-deficient mice showing a reduction in basal neurotransmission reflecting decreased glutamate (i.e., AMPA receptor-mediated) transmission. Long-term potentiation was impaired with no significant change in long-term depression (Bozdagi et al., 2010), and intraperitoneal injection of IGF-1 reversed the electrophysiological and motor deficits seen in the Shank3-deficient mice (Bozdagi et al., 2013).

Our clinical group began prospectively evaluating patients with PMS using standard evaluation tools in 2010; 65 affected individuals have been seen to date at our site and an additional 54 participants have been evaluated across our national PMS network and will be leveraged to meet recruitment goals for this project. We have published descriptive results from 32 patients thus far, 27 of whom (84%) met criteria for ASD using a priori definitions derived from expert consensus commonly used in ASD research (Soorya et al., 2013). Subsequently, we began a controlled trial of IGF-1 in PMS and provided evidence of improvement in core ASD symptoms (Kolevzon et al., 2014) using the Aberrant Behavior Checklist (ABC; Aman et al., 1985) and the Repetitive Behavior Scale-Revised (RBS-R; Bodfish et al., 2000). IGF-1 also reversed phenotypic and electrophysiological changes in human neuronal models of PMS (Shcheglovitov et al., 2013) and iASD (Marchetto et al., 2016), providing additional support for this intervention.

IGF-1 enters the brain from the circulation where it is released mainly by the liver upon growth hormone stimulation. Blood-borne IGF-1 is found in the CNS and promotes brain vessel growth (Lopez-Lopez et al., 2004), neurogenesis, and synaptogenesis (O'Kusky et al., 2000). Once IGF-1 binds to the IGF-1 receptor, activation of the PI3K/mTOR/AKT1 and MAPK/ERK pathways induces its downstream effects (Costales & Kolevzon, 2016). A recent study in Rett syndrome provides evidence of IGF-1 brain penetrance: cerebrospinal fluid and serum analysis revealed significant increases in IGF-1 levels after treatment (Khwaja et al., 2014).

The proposed clinical trial seeks to collect pilot data on the role of exogenous growth hormone in children and adolescents with Phelan McDermid Syndrome to increase IGF-1 levels, which has been shown to have positive effects on social withdrawal, repetitive behaviors, sensory reactivity, and hyperactivity. There is currently no treatment available for PMS and the use of growth hormone may be practical and effective.

Growth hormone binds to its receptor and initiates a cascade of events which involves transcription of several genes resulting in rise of IGF-1. (Vottero et al., 2013, Hormone Resistance and Hypersensitivity; Ashpole et al., 2015, Experimental Gerontology). We hypothesize that increase in IGF-1 stimulated by growth hormone administration should produce the same improvement in behavior in children and adolescents with Phelan McDermid Syndrome as previously demonstrated with use of IGF-1 (Kolevzon et al., 2014).

Growth hormone is an easily available drug whose safety profile has been studied since 1985 (Ranke et al.; 2018). The experience with growth hormone has shown that it is well tolerated by children with few adverse effects as compared to IGF-1. Hypoglycemia is not associated with growth hormone therapy while it is a serious adverse event with IGF-1 therapy, requiring serial monitoring. Growth hormone is also easy to administer as a once daily subcutaneous dose compared to the twice daily subcutaneous injections for IGF-1.

Hence, administration of growth hormone may be a viable option to increase IGF-1 levels and have an impact on the behavior of these children.

Primary and Secondary Study Endpoints

1. Improvement in social withdrawal following growth hormone administration measured using the ABC - Social Withdrawal Subscale and repetitive behavior using the Repetitive Behavior Scale-Revised.

2.Improvement in other behavioral scales following growth hormone administration, such as the Short Sensory Profile, Sensory Assessment for Neurodevelopmental Disorders, and the ABC-Hyperactivity subscale as seen with the IGF-1 trial.

2. VEPs will show improvement in amplitudes in children with Phelan McDermid Syndrome following 12 weeks of growth hormone therapy, similar to the changes seen following IGF-1 therapy.

Protocol Was Already Approved by the Icahn School of Medicine at Mount Sinai (ISMMS) Institutional Review Board (IRB) Under a Different Principal Investigator	No

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Protocol Was Previously Submitted to an External(non-ISMMS) IRB	No

4. Research Personnel

Name/Department	Role/Status	Contact	Access	Signature Authority	Phone	Email
Swathi Sethuram / Pediatrics	PI /	Yes	EDIT			
Robert Rapaport / Pediatrics	Co-Investigator /	Yes	SIGNAUTH		212-241-8487	
Alexander Kolevzon / Psychiatry	Co-Investigator /	Yes	SIGNAUTH		212-659-9134	

5. Sites

Site Name	Icahn School of Medicine at Mount Sinai
Other External Site Name	
Contact Details	
Approved	
Approval Document	
Funded By Mount Sinai	
Other IRB	

6. Subjects - Enrollment

Site Name	Icahn School of Medicine at Mount Sinai
Subjects To Be Enrolled	
20	
Total Number of Subjects to be Enrolled Across All Listed Sites Above (Auto Populated)	20

7. Subjects - Setting and Resources

Setting of Human Research Other

Specify Other Setting of Human Research

Seaver Autism Center for Research and Treatment at Icahn School of Medicine at Mount Sinai

Total Number of Subjects Needed To Complete Study 20

Feasibility of Meeting Recruitment Goals

Power is calculated for differences in baseline to week 12 change scores. Testing for treatment x time interactions and # at .05, we have 80% power to detect moderate to large effects.
Based on data from our previous clinical trial of IGF-1 in patients with Phelan McDermid Syndrome, a 12 week study was feasible in 9 patients.
We feel that 20 patients would provide adequate data to establish the utility of growth hormone in this population. The Seaver Autism Center has access to this population of children with Phelan Mcdermid Syndrome which should help facilitate recruitment.

Facilities To Be Used for Conducting Research

Seaver Autism Center at Icahn School of Medicine
Pediatric Endocrinology & Diabetes Outpatient Clinic at Mount Sinai

Multi-Center Study No

Community-Based Participant Research Study No

PI must attest to the following.
**** Process is adequately described to ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.***

8. Subjects - Populations

Inclusion Criteria

Diagnosis: Pathogenic deletions or mutations of the SHANK3 gene confirmed by array CGH and/or direct sequencing.

Age Range: Cases will be between 2 and 12 years old at the time the phenotypic measures were collected.

Exclusion Criteria

Cases will be excluded if any of the following criteria are applicable:
- closed epiphyses;
- active or suspected neoplasia;
- intracranial hypertension;
- hepatic insufficiency;
- renal insufficiency;
- cardiomegaly/valvulopathy;
- history of allergy to growth hormone or any component of the formulation (mecasermin);
- history of extreme prematurity (<1000 grams) with associated early neo-natal complications, e.g. intra-cerebral hemorrhage, prolonged hypoxia, prolonged hypoglycemia;
- patients with comorbid conditions who are deemed too medically compromised to tolerate the risk of experimental treatment with growth hormone.
- Patient with visual problems that preclude the use of VEPs

Enrollment Restrictions Based Upon Gender, Pregnancy, Childbearing Potential, or Race Yes

Justify Restriction(s)

We will only recruit children between 2 to 12yrs of age and pregnant women will be excluded from the study since this is a pilot clinical trial of GH in children with Phelan McDermid Syndrome.

Age Range(s) Newborn to 8 Years, 9 to 17 Years

Targeted Population(s) Children

Individuals Under 18 Consenting for Themselves Under NYS Law? No

In most cases this does not apply. Typically subjects under 18 assent and a parent (or two) consents for the subject to be in research. This is only for very limited scenarios where the study is related to services/treatment (usually limited to reproductive health, substance abuse or mental health issues) that those under 18 can obtain without parental involvement in NYS and where there was no parental involvement for the related clinical services. See SOP-013 (point 3.2) for additional information.

Other Aspects that Could Increase Subjects Vulnerability

Informed consent shall be obtained from parents or legal guardians of patients with Phelan McDermid Syndrome who typically have global developmental delays and are cognitively impaired.

Safeguards to protect Subjects rights and welfare

Participants suitable for the study will undergo comprehensive medical evaluation by the study psychiatrist. Medical history, family history, physical and neurological examination (including anthropometric measurements, fundoscopic exams), routine hematology and blood chemistry (including liver profile) and X-ray will be performed at baseline. Patients will be monitored for tolerability every 4 weeks throughout the study using physical and neurological examination (including anthropometric measurements and fundoscopic exams). Patients will be monitored at weeks 4, 8, and 12 and then again 4-weeks after study termination with the following safety measures: physical and neurological examination (including anthropometric measurements and fundoscopic exams), routine hematology and blood chemistry.

Potential adverse events from Growth Hormone (GH) will be explained to participant's families and also be monitored for during their serial evaluations.

Informed consent shall be obtained from parents or legal guardians after a thorough explanation of the study protocol.

The study will be conducted according to Good Clinical Practice (GCP), the 1996 Declaration of Helsinki (Protocol Appendix A), (US 21 CFR Part 50—Protection of Human Subjects, and Park 56—Institutional Review Boards) and local rules and regulations of the country.

9. Subjects - Participation

Duration of an Individual Subjects Participation in the Study

Approximately 6 months or lesser

Duration Anticipated to Enroll All Study Subjects

15 months

Estimated Date for the Investigators to Complete This Study Within two years

Procedures for Subjects to Request Withdrawal

Indications to halt active participation of the subject in the GH study
1. Withdrawal of Consent : Patient families may withdraw consent at any time during the course of the study.

To avoid bias, all analyses will include all subjects, including those withdrawn from the study, regardless of adherence to study protocol. If there is doubt concerning a subject's safety, the default mode must be withdrawal from treatment or active study participation, followed by close observation (safety follow up visits) and recommendation of standard treatment.

Return of a subject to active study participation will not be permitted, except if a transient clinical or laboratory abnormality unrelated to study treatment has occurred and subsequent permission to return the patient to active study has been provided.

If a subject is withdrawn from active study during Growth Hormone treatment, they will be returned to the referring physician and standard care will be recommended; in addition, we will request the subject's participation in an end-of-study visit.

Procedures for Investigator to Withdraw Subjects

Indications to halt active participation of the subject in the GH study

1. PI or any regulatory authority (IRB, or FDA) believe withdrawal is necessary for the subject's health, well-being, or best interests.
2. PI or any regulatory authority believe that withdrawal is necessary for the subject's health, well-being, or best interests
3. Laboratory: any abnormality on any test with adverse event (AE, Common Terminology Criteria for Adverse Events, National Cancer Institute, scales) # 3 or greater at any time in the study
4. Any AE of any sort (clinical, laboratory) # 4 will result in halting for the individual and also for the study as a whole.

Participants Will Be Recruited Yes

Recruitment Method(s) Clinical Practice, Other Website

How Participants Will Be Identified

All participants must be diagnosed with Phelan McDermid Syndrome.
Phenotype definition will be conducted using a comprehensive assessment battery, including: (1) psychiatric evaluation; (2) clinical genetics evaluation; (3) neurological examination; (4) Vineland Adaptive Behavior Scales.

All patients must also have pathogenic deletions or mutations of the SHANK3 gene confirmed by array CGH and/or direct sequencing on record.

Who Will Initially Approach Potential Participants Study Personnel, Member of Primary Care Team, Treating Physician, Clinic Personnel

How Research Will Be Introduced to Participants

Potential participants in the Seaver Autism Center outpatient clinic as well as families of patients with Phelan McDermid Syndrome will be informed about this study directly or via websites (such as Phelan McDermid Syndrome Foundation)

How Participants Will Be Screened

Participants will be screened based on the inclusion criteria and a diagnosis of Phelan McDermid Syndrome and with open epiphyses as evidenced by a bone age x ray.

10. Subjects - Risk and Benefits

Risks to Subjects

Growth hormone will be administered as subcutaneous injections once daily by parent or guardian at home.

Blood draws will be done every 4 weeks during study and 4 weeks following study.

Potential adverse events from Growth Hormone(GH) are described in the package insert. Some adverse effects include headaches, myalgia, fluid retention, benign intracranial hypertension, slipped capital femoral epiphyses, insulin resistance and hypothyroidism. Local reactions include erythema or pain at injection site and lipoatrophy with long term use.

Patients will require to be seen by a physician at our center every 4 weeks for evaluations and monitoring safety.

Description of Procedures Taken to Lessen the Probability or Magnitude of Risks

Participants suitable for the study will undergo comprehensive medical evaluation by the study psychiatrist. Medical history, family history, physical and neurological examination (including anthropometric measurements, fundoscopic exams), routine hematology and blood chemistry and X-ray will be performed at baseline. All families will be educated on appropriate growth hormone administration. Patients will be monitored for tolerability every 4 weeks throughout the study using physical and neurological and psychological evaluations (including anthropometric measurements, fundoscopic exams). This monitoring will occur at weeks 4, 8, and 12 and then again 4-weeks after study termination.
All testing will be scheduled at the same time as the four weekly visit in order to avoid inconveniencing patient.

Provisions for Research Related Harm / Injury

Serial evaluations by physician every 4 weeks during study and also safety parameters monitored by blood draws will reduce research related harm/injury.

An adverse event (AE) will be defined as any untoward medical occurrence in a study subject, temporally associated with the use of the experimental medication, whether or not considered related to the medication. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the experimental medication. A serious adverse event (SAE) will be defined as an AE that meets any of the following criteria:
results in death;
is life threatening;
requires inpatient hospitalization;
results in a persistent or significant disability/incapacity;
any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above.

Adverse Events Reporting
The Principal Investigator (PI) will be responsible for the detection and documentation of events meeting the criteria and definition of an adverse event or serious adverse event, as provided in this protocol. During the study, when there is a safety evaluation, the investigator or team member will be responsible for reporting adverse events and serious adverse events. Each subject's parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

Clinical laboratory parameters and other abnormal assessments qualifying as adverse events and serious adverse events:
Abnormal laboratory findings or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Medically attended visits
For each AE the subject experiences, the subject's parents/guardians will be asked if they received medical attention defined as hospitalization, an emergency room visit or a visit to or from medical personnel (medical doctor/doctor of osteopathy or nurse practitioner) for any reason. This information will be recorded in the CRF (case report form).

Lack of Efficacy
Lack of efficacy per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

Time Period, Frequency, and Method of Detecting AEs:
All AEs occurring from the initiation of therapy until 4 weeks following its completion will be recorded on the Adverse Event form in the subject's CRF, irrespective of severity or whether or not they are considered medication-related. Onset of chronic illness (e.g. autoimmune disorders, asthma, type 1 diabetes and allergies) and conditions prompting emergency room (ER) visits or physician office visits that are not related to well-child care, injury, or common acute illnesses (e.g., upper respiratory tract infection, otitis media, pharyngitis, and gastroenteritis) will be reported during the entire study period. The investigator will inquire about the occurrence of AEs at every visit/contact during the study and throughout the follow-up phase as appropriate. All AEs either observed by the investigator or a clinical collaborator or reported by the subject's parent/guardian spontaneously or in response to a direct question will be evaluated by the investigator. AEs not previously documented in the study will be recorded in the Adverse Event form within the subject's CRF. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to drug administration should be established. Details of any corrective treatment should be recorded on the appropriate page of the CRF.

When an AE/SAE occurs, it will be the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostic reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF or SAE Report Form as applicable. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information.

Safety: To evaluate safety, participants will be assessed every 4 weeks by the study psychiatrist. There are a number of tertiary outcomes designed to monitor the safety of GH.

Monitoring for AEs will be conducted during scheduled and unscheduled visits per clinical and laboratory assessments. General AEs will be graded by the National Cancer Institute (NCI) CTCAE scales (note: please see discussion immediately following for AEs with neurological signs and symptoms). Examples of possible AE grades for parameters which will be measured during treatment (shown in Table 3 Research Protocol PDF). Also, any AE that the PI deems serious, although not easily categorized in the National Cancer Institute grading system, will be considered # grade 3.

If a subject develops significant (CTCAE AE # 3 grade) neurological signs and symptoms (e.g. cerebrovascular event or peripheral neuropathy), they will be seen immediately for a comprehensive evaluation, appropriate treatment, and removal from active participation in the study. We will also apply NCI-CTCAE criteria for attribution of AE by means of the following descriptors and codes, following the NCI guidelines for their application.

unrelated to treatment 1
unlikely related to treatment 2
possibly related to treatment 3
probably related to treatment 4
definitely related to treatment 5

The following are the potential adverse events associated with GH and how we intend to monitor and prevent these occurrences.

Slipped capital femoral epiphyses (SCFE)
SCFE is a potential adverse effect of growth hormone therapy. We will monitor for this by parental reporting of hip pain (unilateral or bilateral), limping or difficulty bearing weight. Children suspected of SCFE will undergo bilateral hip x-ray in a frog leg position for diagnosis.

Alterations in glucose homeostasis
Glucose homeostasis will be measured using hemoglobin A1C levels as well as glucose and insulin levels prior to and during therapy.

Increased intracranial pressure
In order to monitor for increased intracranial pressure, children will undergo fundoscopic examination.

Expected Direct Benefit to Subjects

Autism is a severe lifelong neuro-developmental disorder characterized by impairments in reciprocal social interaction, communication deficits and repetitive and restricted patterns of behavior and interests with onset in the first three years of life.

Our pilot study on use of IGF-1 in patients with Phelan McDermid syndrome showed improvement in the standardized Aberrant Behavior Checklist (ABC) and the Repetitive Behavior SubScale-Revised (RBS-R) after 12 weeks of therapy (Kolevzon, 2014).

Considering growth hormone acts via the IGF-1 pathway, this medication that is easily accessible and administered once daily (in comparison to twice daily IGF-1) should improve social withdrawal in this population. Growth hormone will also not produce hypoglycemia in patients that has been known to occur with IGF-1 use.

Benefit to Society

Growth hormone is a commercially available drug that has a good safety profile following decades of study. Growth hormone administration has been shown to improve mental and motor development in children with Prader Willi Syndrome owing to its impact on IGF-1 (Donze et al, 2018).

The success of this clinical trial could have implications on other genetic forms of autism spectrum disorder in the future. It will also provide more information to the healthcare community in this field.

Provisions to Protect the Privacy Interests of Subjects

Members of the research team may also provide clinical care to this population in the Seaver Autism Center; thus, it is acceptable and appropriate for the team to present the research to patients in the clinic. Patients recruited outside of the Seaver Autism Center will approach study personnel after viewing our ads and only if the family is willing will our research personnel discuss the study with family. We may conduct initial telephone conversations with these families to inform them regarding the study. Prospective subjects and their parents will be informed of and consented for the study in the privacy of an investigator's office during a clinic visit. Follow-up visits and phone calls made to subjects will be carried out in the context of clinical care.

It will be explained to the subject's parents that all questions asked and procedures performed will be part of the study, and they will be informed that they do not need to answer all of the questions or they can decline a procedure if they feel uncomfortable.

Economic Impact on Subjects

None

11. Subjects - Children

Select Which of the Following Best Describes the Risk Presented to Children
**** No greater than minimal risk to children is presented.***
**** Greater than minimal risk to children and the research presents the prospect of direct benefit to the individual subjects.***
**** Greater than minimal risk to children presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject.***
**** None of the above but the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.***

Risk Presented to Children	Greater Than Minimal Risk With Direct Benefit

12. Procedures - Narrative

Description of the Study Design

The proposed pilot will seek to recruit 20 children aged 2 to 12 years old with SHANK3 deletions or mutations and with radiographic evidence of open epiphyses. Phenotype definition will be conducted using a comprehensive assessment battery, including: (1) psychiatric evaluation; (2) clinical genetics evaluation; (3) neurological examination; (4) Vineland Adaptive Behavior Scales. The study will include newly recruited children in addition to those who have been previously recruited for the purposes of genetic studies by the Seaver Autism Center.

Patients recruited will have screening prior to trial and will then follow up at 4 weeks, 8 weeks and 12 weeks of therapy with growth hormone daily injections. A 4 week post therapy follow up will also be arranged.

Inclusion criteria:
Diagnosis: Pathogenic deletions or mutations of the SHANK3 gene confirmed by array CGH and/or direct sequencing.
Age Range: Cases will be between 2 and 12 years old at the time the phenotypic measures were collected.

Exclusion criteria:
Cases will be excluded if any of the following criteria are applicable:
closed epiphyses;
active or suspected neoplasia;
intracranial hypertension;
hepatic insufficiency;
renal insufficiency;
cardiomegaly/valvulopathy;
history of allergy to growth hormone or any component of the formulation (mecasermin);
history of extreme prematurity (<1000 grams) with associated early neo-natal complications, e.g. intra-cerebral hemorrhage, prolonged hypoxia, prolonged hypoglycemia;
patients with comorbid conditions who are deemed too medically compromised to tolerate the risk of experimental treatment with growth hormone.
Patient with visual problems that preclude the use of VEPs

Drug
Growth hormone is secreted by the somatotrophs of the anterior pituitary gland in a pulsatile manner. It binds to its receptor, signaling a cascade of intracellular events which directly stimulated the synthesis and release of IGF-1. (Ashpole et al; 2014, Grimberg et al; 2016).

Growth hormone is FDA approved for use in children with growth hormone deficiency (including idiopathic [of unknown cause] growth hormone deficiency), Turner syndrome, Noonan syndrome, Prader-Willi syndrome, short stature homeobox-containing gene (SHOX) deficiency, chronic renal insufficiency, idiopathic short stature and children small for gestational age. (https://www.fda.gov/Drugs/DrugSafety/ucm237839.htm)

It is available in the form of several commercial preparations. This is typically available as a 10 mg vial to be reconstituted with in-package syringe of 1 mL of bacteriostatic water (preserved with 0.33% metacresol), and a 25G reconstitution needle.

Drug Administration
Growth hormone will be administered subcutaneously once daily using a 12-week single group design. No placebo will be used. The 12-week duration was selected because of our previous trial with IGF-1 showing effects in standardized behavior scales in that duration, hence establishing proof of concept.

The dose of daily growth hormone varies with the indication for therapy. Approved doses of growth hormone range from 0.16-0.25mg/kg/week for growth hormone deficient patients (Grimberg et al.; 2016) and up to 0.47 mg/kg/week for patients born small for gestational age.

In our proposed trial, we expect a majority of our patients to be growth hormone sufficient and therefore similar to the population of children with idiopathic short stature treated with growth hormone. We will recommend a dose of 0.15mg/kg/week divided daily for 2 weeks as a starting dose to ensure safety and tolerance. The dose will then be increased to 0.3mg/kg/week for 10 weeks, an average growth hormone dose in children with idiopathic short stature.

The growth hormone dose will be titrated based on IGF-1 levels monitored serially up to a maximum dose of 0.45mg/kg/week.(http://www.ferringusa.com/wp-content/uploads/2018/07/ZOMACTON-PI-7-18.pdf)

Drug dose is calculated on a mg/kg/week basis. Using Center for Disease Control average Weight-for-age statistics in typically developing children ages 2 to 12 years (www.cdc.gov/growthcharts/cdc_charts.htm), the overall average weight across a representative sample of males and females in this age range is 24.65kg.

Average growth hormone dose for weeks 1-2: 0.15mg * 24.65kg per week = 3.7 mg per week

Average growth hormone dose for weeks 3-10: 0.3mg * 24.65kg per week = 7.4 mg per week

With a recruitment target of 20 patients, we anticipate the need for a total of 1628 mg of growth hormone with each person requiring about 81 mg of growth hormone in 12 weeks. We anticipate the need for 17 vials of growth hormone (10 mg per vial).

Description of Procedures Being Performed

Description of Phenotypic Measures (See Table 3):
The phenotypic measures include standardized measures such as history and physical, neurologic exam, treatment history, prenatal-perinatal questionnaire as well as the measures listed below.

Vineland Adaptive Behavior Scale (VABS): The VABS is a semi-structured interview designed to measure personal and social sufficiency in individuals from birth to adulthood. It provides a general assessment of adaptive behavior within the sub-domains of Communication, Daily Living Skills, Socialization, and Motor Skills. Administration takes between 20-60 minutes.

Description of Outcome Measures:
Parent-Rated Measures
The Aberrant Behavior Checklist (Aman et al., 1985) is a caregiver report symptom checklist validated and widely used for assessing problem behaviors in children and adults with intellectual disability. Fifty-eight specific items are rated and a manual provides comprehensive descriptions for each assessed behavior. The 58 items resolve into five subscales: Irritability; Lethargy/Social Withdrawal; Stereotypic Behavior; Hyperactivity; Inappropriate Speech.

The Repetitive Behavior Scale-Revised (Lam and Aman, 2007) is a validated tool that captures the breadth of restricted and repetitive behaviors in ASD. The RBS-R has 43 items that resolve into five factors and a total score: Ritualistic/Sameness; Stereotypies; Self Injury; Compulsive Behavior; Restricted Interests. The RBS-R is a continuous measure of the presence and severity of repetitive behaviors. A total score is generated, with higher scores indicating more restricted, repetitive and stereotyped behaviors but each subscale independently shows adequate psychometric properties and acceptable reliability and validity.

The Sensory Profile (Dunn, 1999) is a caregiver questionnaire which measures responses to sensory experiences in everyday life. There are 125 items in the full Sensory Profile, and there is a short version which contains 38 items commonly used in research settings. Sensory processing subscales on the Short Sensory Profile (SSP) include tactile sensitivity, taste/smell sensitivity, visual/ auditory sensitivity, movement sensitivity, low energy/ weak, and under-responsivity/seeks sensation. Tactile, smell/taste and visual/auditory sensitivity scores represent a child's ability to respond to respective sensory stimuli in the environment. Parents use a Likert scale to rate how frequently their child demonstrates a particular behavior (ranging from 1 = always to 5 = never). A lower score indicates greater deviation from typically developing children and indicates more sensory reactivity symptoms.

The Caregiver Top Three Concerns is a Visual Analog Scale rating of severity of the top three causes for concern for the caregivers. Caregivers are instructed to identify causes for concern that are related to the individual's PMS.

Clinician-Rated Measures
The PMS Domain Specific Concerns is a Visual Analog Scales that assesses domain specific individualized items that are identified as key areas of impairment by caregivers. The domains that are assessed are: Social Withdrawal, Repetitive Behaviors, Speech and Language, Anxiety, Motor Performance, Sensory Reactivity, and Cognition. The identified concerns should be related to the subject's PMS.

The Clinical Global Impression – Severity of Illness (CGI-S) and Clinical Global Impression – Improvement of Illness (CGI-I; Guy, 1976) are brief, easy to administer, clinician-rated measures. The CGI-S asks the clinician to rate the patient's current severity of illness based on the clinician's clinical experience with the relevant population. The CGI-S is rated on a 7-point scale, with a range of responses from 1 (normal, not at all ill) through 7 (amongst the most extremely ill patients). The CGI-I asks the clinician to rate the patients' total improvement since baseline, whether or not the improvement is judged to be due entirely to the experimental treatment. The CGI-I is rated on a 7-point

scale, with a range of responses from 1 (very much improved) to 7 (very much worse). For both the CGI-S and the CGI-I, the clinician is allowed to use all available information at the time of the rating. The CGI-I has emerged as a convention for bifurcating clinical trial subjects into "responders" (i.e. a CGI-I of 1 or 2) and "non-responders" (i.e. a CGI-I of 3 to 7) (Busner et al., 2009). In this application, the CGI-I can be a useful tool for gaining a general overview of the therapeutic potential of an experimental treatment. We will improve the sensitivity of the CGI-S and –I by using anchor points that are specific to the signs and symptoms of FXS and train all sites in the application.

Peabody Picture Vocabulary Test (PPVT): This is a wide-range measure of receptive language for standard English that is administered by a clinician to children in the 2-6 age range. It takes 10-15 minutes to administer.

Objective Measures

Visual Evoked Potentials (VEPs) provide a noninvasive technique to evaluate the functional integrity of visual pathways in the brain from the retina to the visual cortex via the optic nerve/optic radiations. The VEP is recorded from the head's surface, over the visual cortex, and is extracted from ongoing EEG through signal averaging. VEPs reflect the sum of excitatory and inhibitory postsynaptic potentials occurring on apical dendrites (Zemon et al., 1986) which modulate excitatory and inhibitory signals received by the pyramidal cells. The major positive and negative peaks and troughs in VEP waveforms reflect different cellular events. The contrast-reversing checkerboard stimulus used in this study produces a positive peak at approximately 60 ms (P0 or P60), reflecting activation of the primary visual cortex from the lateral geniculate nucleus. A negative peak at approximately 75 ms (N0 or N75) reflecting depolarization and glutamatergic postsynaptic activity spreading to the superficial layers of primary visual cortex, and a positive peak at approximately 100 ms (P1 or P100) reflecting superficial hyperpolarization and GABAergic activity (Zemon et al., 1980). VEPs have been used in clinical trials; for example, an antiepileptic drug (gabapentin; Conte et al., 2009) and an infant formula (O'Connor et al., 2001); both received FDA approval based in part on positive findings from VEP studies. Data from ongoing clinical trials at Mount Sinai provide support for use of VEPs as a measure of treatment response.

Auditory Event Related Potentials (AERPs) are useful for characterizing early processing of auditory tones and habituation to rapidly repeated stimuli as in speech processing. Tones are presented in rapid succession (e.g., up to every 500 ms) and ERP components to both initial stimulus presentations and their habituation to subsequent stimuli (i.e., reduction in amplitude) are examined. Auditory gating waveforms have been well characterized across development (Milner at l., 2014; Tremblay et al., 2014; Magnee et al., 2011) and are comprised of a fronto-central peak 100 ms after the onset of the auditory stimulus (N1) and a subsequent positive peak (P2) reflecting activity in auditory cortex, mesencephalitic reticular activating system, planum temporale, and auditory association cortex (Crowley et al., 2004; Godey et al., 2001). The N1-P2 complex reflects two distinct components: initial stimulus processing (N1) and subsequent attention to and processing of stimulus information (P2). P2 also has been implicated in speech processing (Knowland et al., 2014; Klucharev et al., 2003) suggesting that its analysis may be important for understanding neurophysiological mechanisms associated with broader cognitive and language developmental dysfunctions in FXS. Recent AERP studies suggest that measures of auditory gating may provide a sensitive and selective probe of sensory physiology in FXS (Hall et al., 2009). Individuals with FXS, for example, show auditory hypersensitivities consistent with Fmr1KO mouse models of local-circuit hyper-excitability involving prolonged "UP" states in the gamma frequency range, decreased glutamatergic drive on fast-spiking GABAergic inhibitory neurons in sensory cortex, and heightened neurophysiological response to auditory stimuli (Rotschafer et al., 2013).

The Sensory Assessment for Neurodevelopmental Disorders (SAND) is a clinician-administered assessment and corresponding caregiver interview that is not dependent on verbal or cognitive ability and is therefore appropriate for severely affected or nonverbal individuals with FXS. The algorithm measures sensory discrete hyperreactivity, hyporeactivity, and seeking behaviors across visual, tactile, and auditory domains. The SAND has also been validated in ASD with significant correlation to the previously validated Sensory Profile. Results from our preliminary data suggest the SAND can identify sensory reactivity subtypes that differentiate FXS and other forms of ASD.

Eye tracking will utilize three tasks to measure attention in general and social attention specifically. (1) The Visual Paired Comparison task presents two identical stimuli (faces or patterns) side by side for familiarization. The familiar stimulus and a new stimulus are then paired on test and recognition is inferred from preferential looking to the new target. (2) The Gap-Overlap task measures the latencies of gaze shifts from a central fixation point to a peripheral target are under 2 conditions. During gap trials, the fixation cross disappears prior to the onset of the peripheral cue, whereas in the overlap condition, the fixation cross remains on the screen throughout the trial. Saccadic latencies are typically greater for overlap than for gap trials since the former requires disengagement of attention in addition to orienting to a target (gap effect). (3) Flicker measures the temporal resolution of attention. Four squares that flicker from black to white are presented against a grey background. The target square flickers 180 degrees out-of-phase from the three distractors. Flickering occurs at 1 of 4 frequencies: 0.2, 0.5, 1, or 2 Hz. A preference for the target square indicates phase individuation, which is easier at slower frequencies. Participants are required to look at a screen for approximately 10 minutes while images of human faces will be presented and automated assessments of time spent looking at socially salient features of test images are recorded.

Description of the Source Records that Will Be Used to Collect Data About Subjects

Data will be collected from patient's medical records including history and physical examinations, laboratory and radiological information and psychiatric evaluations. We use EPIC as electronic medical record system. Patient information from the past will also be available on EPIC such as past medical records. A confidential data set will be maintained electronically to store patient information with separate study ID's for patients to maintain their confidentiality.

Description of Data that Will Be Collected Including Long-Term Follow-Up

These patients will be followed in the Seaver Autism Center four weeks post therapy and will continue to follow at this center if they are patients here. If not, they will return to their primary providers for standard care.

Research Requires HIV Testing No

13. Procedures - Genetic Testing

Genetic Testing Will Be Performed No

Guidance and Policies > Future Use Data Sharing and Genetic Research

14. Procedures - Details

Surveys or Interviews Yes

Type of Instruments Being Used Standardized

Names of Standardized Instruments

Vineland Adaptive Behavior Scale (VABS)

Description of Outcome Measures:
Parent-Rated Measures
The Aberrant Behavior Checklist
The Repetitive Behavior Scale-Revised (RBS-R)
The Sensory Profile
The Caregiver Top Three Concerns

Clinician-Rated Measures
The PMS Domain Specific Concerns
The Clinical Global Impression – Severity of Illness (CGI-S) and Clinical Global Impression – Improvement of Illness (CGI-I)
Peabody Picture Vocabulary Test (PPVT)

Objective Measures
Visual Evoked Potentials (VEPs)
Auditory Event Related Potentials (AERPs)
The Sensory Assessment for Neurodevelopmental Disorders (SAND)
Eye tracking

Audio / Photo / Video Recording No

Deception No

Results of the Study Will Be Shared with Subjects or Others No

15. Procedures - Compensation

Compensation for Participation No

16. Consent - Obtaining Consent

Consent Process Parental Permission / Child Assent

Where and When Consent Will Be Obtained

The investigator will describe the protocol to potential subjects' parents/guardians in person, although general information and assessment for eligibility can be carried out by phone if necessary. The Informed Consent may be read to the subjects' parent/guardians, but, in any event, the investigator or designee shall give the subjects' parents/guardians ample opportunity to inquire about details of the study and ask any questions before dating and signing the Informed Consent Form. The Informed Consent will be created with a level of language fully comprehensible to the prospective subjects' parents/guardians. Informed consent will be documented by the use of a written consent form approved by the IRB and signed and dated by the subjects' parents/guardians and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form will be kept on file by the investigator for possible inspection by regulatory authorities. The parents/guardians will receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects' parents/guardians, and will receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to subjects' parents/guardians.

Waiting Period for Obtaining Consent

Two weeks

SOP HRP-090 Informed Consent Process for Research Is Being Used Yes

PPHS Worksheets, Checklists and SOPs

Process to Document Consent in Writing Will Use Standard Template

Non-English Speaking Participants Will Be Enrolled No

Justification for Not Enrolling Non-English Speaking Participants

We will have our consenting forms only in English and do not want to enroll participants unable to understand English since it will not be fair for them to not have a complete understanding of the study. The various scales being used in the study are also available in English. Since this is only a pilot trial with 20 patients, we will enroll English speaking patients for this particular trial.

17. Consent - Parental Permission

Permission To Be Obtained From	One Parent
Parental Permission Document	GH Consent version date 02-26-19.docx
Assent To Be Obtained From	None of the Children
Which of the Following Are True (Choose At Least One)	The capability of these children is so limited that they cannot reasonably be consulted.

18. Consent - Documents

Consent Documents

Type	Consent form
Name	Consent for GH PMS trial
Upload	GH Consent version date 02-26-19.docx

Consent Templates

19. Data - Collection

Health Related Information Will Be Viewed, Recorded, or Generated	Yes

Description of Health Information That Will Be Viewed, Recorded, or Generated

We will view, record and generate information on patient's age, clinical status based on physical examination findings, laboratory parameters monitored during trial and radiological findings.
We will also generate and record information on psychological assessments of these patients and their VEP's results during the trial.

Non-Health Related Information Will Be Viewed or Recorded	Yes

Description of Non-Health Information That Will Be Viewed or Recorded

Patient's name, demographic information including address, telephone number will be viewed and recorded.

HIV / AIDS Related Information Will Be Viewed or Recorded	No
Data That Will Be Viewed, Recorded, or Generated Contains ANY of the Following Directly Identifiable Information	Yes
Will Be Viewed	Name, Medical Record Number, Address by street location, Telephone number, All Elements of Dates for Dates Directly Related to an Individual (i.e., Birth Date, Admission Date, Discharge Date), Email Address
Will Be Recorded	Name, Medical Record Number, Address by street location, Telephone number, All Elements of Dates for Dates Directly Related to an Individual (i.e., Birth Date, Admission Date, Discharge Date), Email Address
Data Collection Sheet	DATA COLLECTION SHEET edited.docx

A Data Collection Sheet is required if you are either performing a retrospective review, or your study meets the category of exempt 4 research, or your study meets the category of expedited 5 research. Please upload it here.

Data Collection Source(s)	Participant, Medical Chart (Paper or Electronic), Clinical Database

20. Data - HIPAA

Obtaining HIPAA Authorization Yes

How PHI Will Be Protected from Improper Use or Disclosure

Data will be stored in a secure data warehouse which will remain confidential. Only members of the study will have access to this information. Patients will be provided with a study ID which will maintain their confidentiality.

PHI Will Be Destroyed at the Earliest Opportunity Consistent with the Research No

Justification for Retaining PHI Indefinitely

This PHI may provide data to establish more long term studies in the field of growth hormone therapy in children with genetic forms of autism to look at its impact on their social withdrawal.

PHI Will Be Shared No

PI must attest to the following.

**** I assure that the protected health information (PHI) will not be disclosed to any other person or entity not listed on this form except where required by law or for the authorized oversight of this research project. If at any time I want to reuse this PHI for other purposes or disclose it to other individuals or entities I will seek approval from the IRB.***

21. Data - Storage

Location Where Data Will Be Stored

Research data will be stored on a Microsoft Excel file on a secure server accessed via secure log-ins and passwords on hospital computers by the named personnel involved in the study. Only members of the research team will have access to the data. The subject will be identified by study number, and the link between the subject's full name and the study number will be stored in a locked room on the 4th floor of the Annenberg building.

How will the data be stored?	With a Code That Can Be Linked to the Identity of the Participant
Research Personnel Responsible for:	Swathi Sethuram
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	Yes
Research Personnel Responsible for:	Robert Rapaport
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	Yes
Research Personnel Responsible for:	Alexander Kolevzon
Accessing Data	Yes
Receipt or Transmission of Data	Yes
Holding Code That Can Be Linked to Identity of Participants	Yes

Duration Data Will Be Stored

10 years

Steps That Will Be Taken to Secure the Data During Storage, Use, and Transmission

Data with PHI will only be stored on hospital computers. Data shared outside hospital networks will only have de-identified information. All data will only be accessible to study personnel.

Power Analysis/Data Analysis Plan (Including Any Statistical Procedures)

The model for this design is baseline to week 12 change scores. To examine whether electrophysiological markers track changes in clinical profiles, we will fit an additional GLMM with VEP values included as a time-varying rather than baseline covariate. If treatment effects become less significant it will suggest that GH is acting on clinical outcomes through the biomarker. Finally, we will directly correlate week-12 change scores for VEP and clinical measures. All tests will use a two-sided # of .05.

Power Analysis

Power is calculated for differences in baseline to week 12 change scores. Testing for treatment x time interactions and # at .05, we have 80% power to detect moderate to large effects.

22. Data - Safety Monitoring

More Than the Minimum Data Safety Monitoring Will Be Done	Yes
Principal Monitor	Swathi Sethuram
Additional Monitors	
Name	Robert Rapaport
Title	Professor
Department	Pediatrics
Contact Details	Work1 Gustave L. Levy PlaceNew YorkNY10029
Type	Team Member
Name	Alexander Kolevzon
Title	Associate Professor of Psychiatry and Pediatrics
Department	Psychiatry
Contact Details	WorkOne Gustave L. Levy PlaceNew YorkNY10029
Type	Team Member

Specific Items That Will Be Monitored for Safety

Adverse effects from growth hormone administration, subject compliance, drop outs

Frequency of Data Review

Data will be reviewed every 4 weeks during trial and thereafter every 3-6 months.

Rules for Alteration of Study Design

Not applicable

Selection Procedures to Minimize Toxicity

Growth hormone will be administered subcutaneously once daily using a 12-week single group design. No placebo will be used. The 12-week duration was selected because of our previous trial with IGF-1 showing effects in standardized behavior scales in that duration, hence establishing proof of concept.

The dose of daily growth hormone varies with the indication for therapy. Approved doses of growth hormone range from 0.16-0.25mg/kg/week for growth hormone deficient patients (Grimberg et al.; 2016) and up to 0.47 mg/kg/week for patients born small for gestational age.

In our proposed trial, we expect a majority of our patients to be growth hormone sufficient and therefore similar to the population of children with idiopathic short stature treated with growth hormone. We will recommend a dose of 0.15mg/kg/week divided daily for 2 weeks as a starting dose to ensure safety and tolerance. The dose will then be increased to 0.3mg/kg/week for 10 weeks, an average growth hormone dose in children with idiopathic short stature. The growth hormone dose will be titrated based on IGF-1 levels monitored serially up to a maximum dose of 0.45mg/kg/week.(http://www.ferringusa.com/wp-content/uploads/2018/07/ZOMACTON-PI-7-18.pdf)

Drug dose is calculated on a mg/kg/week basis. Using Center for Disease Control average Weight-for-age statistics in typically developing children ages 2 to 15 years (www.cdc.gov/growthcharts/cdc_charts.htm), the overall average weight across a representative sample of males and females in this age range is 30kg.

Average growth hormone dose for weeks 1-2: 0.15mg * 30kg per week = 4.5mg per week = 0.6mg per day

Average growth hormone dose for weeks 3-10: 0.3mg * 30kg per week = 9mg per week = 1.3 mg per day

Grading System to Evaluate Adverse Events

We will apply NCI-CTCAE criteria for attribution of AE by means of the following descriptors and codes, following the NCI guidelines for their application.

unrelated to treatment 1
unlikely related to treatment 2
possibly related to treatment 3
probably related to treatment 4
definitely related to treatment 5

Procedures to Assure Data Accuracy

Data will be stored only by study personnel and will be cross checked twice prior to saving data.

Suspension Reported to

IRB and GCO

Anticipated Circumstances of Subject Withdrawal

The following criteria will be used to identify possible adverse treatment events, which will indicate the need to halt active participation of the subject in the GH study
Withdrawal of Consent PI or any regulatory authority (IRB, or FDA) believe withdrawal is necessary for the subject's health, well-being, or best interests.

PI or any regulatory authority believe that withdrawal is necessary for the subject's health, well-being, or best interests.

Laboratory: any abnormality on any test with adverse event (AE, Common Terminology Criteria for Adverse Events, National Cancer Institute, scales) # 3 or greater at any time in the study.

Any AE of any sort (clinical, laboratory) # 4 will result in halting for the individual and also for the study as a whole.

Primary or Secondary Safety Endpoints

The study will be halted* if two patients experience stopping conditions. (Exceptions for this criterion: Patients who withdraw voluntarily for reasons not directly related to or intrinsic to the study, e.g. incidental considerations such as concerns about travel time to study visits, unexpected pregnancy in the family, etc. Clearly, patients who experience adverse effects during growth hormone treatment would count towards this criterion for whole study stopping).

In addition, the study will be halted if one patient experiences a serious related adverse effect (grade # 4 AE).

All safety data will be reported to the IRB, and FDA every six months, or, in the case of any major safety concern or question, immediately. If any study stopping condition occurs, this will be reported immediately and the study halted, pending review by IRB, and FDA, and until the decision by regulatory authorities to resume, suspend or close the study has been made.

*Operationally, "halting" will ordinarily mean that no further screening of new subjects and no treatment initiation will occur until the safety issue has been investigated and resolved (i.e., a final decision has been made to resume, suspend or close the study has been made). Enrolled study participants who have no new symptoms or adverse effects will ordinarily be allowed to continue study observation or treatment without interruption while the safety issue is being investigated, unless it is the contemporaneous judgment of the PI or subsequent judgment of the IRB, or FDA that it is unsafe to do so, in which case all observation or treatment interventions will be suspended forthwith.

Data Monitoring Committee Description	Data Monitoring Committee.docx
DMC Charter Available	No
Will the Research Include Data Coordinating Center Activities?	No

23. Funding

Funding Source Name	Seaver Foundation
Contact	
Funding Category	Foundation
Meditrack (https://contracts.tractmanager.com/Contracts/Login.aspx)	Meditrack (https://contracts.tractmanager.com/Contracts/Login.aspx)
Grant or Contract Title	An Open Label Trial of Growth Hormone in Children and Adolescents with Phelan-McDermid Syndrome Targeting Social Withdrawal and Repetitive Behavior
Grant or Contract Number	
Funding Status	Funded
Project Initiated By	Investigator
Grant / Contract Principal Investigator (PI)	Swathi Sethuram
Department	Pediatrics
Department	Pediatrics
Phone	
Email	swathi.sethuram@mountsinai.org
Protocol and Funding Proposal Match	Yes
Identify Substantive Differences Between Protocol and Funding Proposal	

24. Radiation Safety

Study protocol involves any of the following Radiological Procedures requiring use of Dosimetry Chart	Yes

**** Radiological procedures that are administered in addition to those that the participant would receive as part of standard care (radiation above and beyond standard of care)***
**** Radiological procedures that are administered solely for experimental or research purposes (would NOT be otherwise administered)***
**** Standard of care radiological procedures that are being altered or performed differently for research***
**** Use of radiological procedures that are the subject of the investigation (comparison studies)***

Dosimetry Chart
Please fill out the chart and attach it below.

Dosimetry Chart	DOSIMETRY.xlsx
Study protocol involves any of the following Radiological Procedures	No

**** Use of an investigational radiopharmaceutical, or use of an approved radiopharmaceutical for an investigational purpose***
**** Use of investigational radiotherapy, or use of approved radiotherapy for an investigational purpose***
**** Use of fluoroscopy***
**** Radiation exposure to children or pregnant women***
**** Radiation exposure to healthy subjects (ADULTS)***
**** Use of an investigational radiologic device (such as an experimental scanner), or use of an approved device for an investigational purpose***

Study protocol involves any of the following Standard of Care Radiological Procedures (including projects where discrete Standard of Care Imaging is acquired in addition to Research Imaging)	Yes

**** CT imaging***
**** Nuclear medicine***
**** Radiography***
**** Fluoroscopy***
**** Radiation-based therapy***
**** PET/CT***

25. Drugs / Biologics

Study Fund Account (or alternate departmental / fund account, if study is not yet established)	[redacted]
Generic Name	Recombinant Human Growth Hormone (Somatropin)
Brand Name	Uncertain at this point
Drug Has Valid IND	No
	For each drug / biologic with an IND number, ensure that the application includes one of the following. * Sponsor protocol with the IND number. * Communication from the sponsor or the FDA with the IND number.
IND Number	
Name of IND Holder	
Type of IND Holder	
Drug Meets One of the Following Categories for Exemption	Yes
	Category 1: * The drug is lawfully marketed in the United States. * The research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug. * The research is not intended to support a significant change in the advertising for the product. * The research does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug. * The research is conducted in compliance with the marketing limitations described in 21 CFR §312.7. Category 2: * A clinical investigation for an in vitro diagnostic biological product that involves one or more of the following: (1) Blood grouping serum; (2) Reagent red blood cells; or (3) Anti-human globulin. * The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure. * The diagnostic test is shipped in compliance with 21 CFR §312.160. Category 3: * A clinical investigation involving use of a placebo when the investigation does not otherwise require submission of an IND.
Category for Exemption	Category 1
Justification for Meeting Criteria	Growth hormone is FDA approved for use in children with growth hormone deficiency (including idiopathic [of unknown cause] growth hormone deficiency), Turner syndrome, Noonan syndrome, Prader-Willi syndrome, short stature homeobox-containing gene (SHOX) deficiency, chronic renal insufficiency, idiopathic short stature and children small for gestational age. (https://www.fda.gov/Drugs/DrugSafety/ucm237839.htm) This research is intended as a pilot clinical trial to look at social withdrawal and repetitive behavior in children with PMS and not as a new indication for GH treatment. Our study population will not have growth hormone administered for any of the FDA approved indications. The results of this study may warrant further such studies in the future. The dose of daily growth hormone varies with the indication for therapy. Approved doses of growth hormone range from 0.16-0.25mg/kg/week for growth hormone deficient patients (Grimberg et al.; 2016) and up to 0.47 mg/kg/week for patients born small for gestational age. In our proposed trial, we expect a majority of our patients to be growth hormone sufficient and therefore similar to the population of children with idiopathic short stature treated with growth hormone. We will recommend a dose of 0.15mg/kg/week divided daily for 2 weeks as a starting dose to ensure safety and tolerance. The dose will then be increased to 0.3mg/kg/week for 10 weeks, an average growth hormone dose in children with idiopathic short stature. We will obtain an exemption from the FDA IND for the use of growth hormone in this study. Neither the patients nor their insurances will be charged for growth hormone. The medication will be funded by the study and provided to families to administer daily at home.

	To be a coordinating center, the Mount Sinai investigator is the Principal Investigator for multi-site participation in the trial. The Investigational Drug Service (IDS) may support trials as the coordinating center. IDS services include but are not limited to randomizing for other sites, storing and shipping drugs to participating sites, etc.
Icahn School of Medicine at Mount Sinai (ISMMS) Is the Coordinating Center	Yes
Role of the Investigational Drug Service (IDS)	Not applicable, single center study
Drug / Biologic Description (Manufacturer/Generic Name/Form/Strength)	Somatropin/recombinant Human Growth Hormone as a subcutaneous injection, typically sold commercially as 10mg/vial
Controlled Substance	No
Schedule	
	In order for the Icahn School of Medicine at Mount Sinai (ISMMS) to be compliant with the regulations regarding controlled substance research, a New York State Department of Health-issued Researcher license and DEA-issued Researcher Registration Number must be on file for each trial using controlled substances. The Investigational Drug Service maintains these licences and will make them available to our investigators to support our research. Refer to www.health.state.ny.us/professionals/narcotic and http://firstclinical.com/journal/2011/1112_DEA.pdf for more information.
Using Investigational Drug Service (IDS) Research License	
Use of this Drug / Biologic Is Considered Standard of Care	No
Requested Pharmacy Services	Dispensation, Storage, Label
Specify Other Requested Pharmacy Services	
Drug / Biologic Will Be Supplied By	Commercially Available/Sourced by Hospital
Specify Other Drug / Biologic Supplier	
Using Placebo	No
Placebo Will Be Supplied By	
Compounding Required (Paid for by Study Funds)	
Where Drug / Biologic Will Be Administered	Outpatient Clinic
Specify Location of Private Office	
Storage Requirements of Drug / Biologic	Refrigerated (2-8°C)
Where Drug / Biologic Will Be Stored	Patients Own Supply
ALL of the Following Storage Criteria Are Met	
	* The storage area is well maintained, provides adequate lighting, ventilation, sanitation, space and security. * The temperature in the storage area is controlled and monitored using calibrated monitoring devices. * The temperature monitoring system has sensors

	for continuous monitoring and alarms set at the points representing the temperature extremes. * Records of temperatures and alarms are maintained and all excursions outside the labeled storage conditions are appropriately investigated and reported to the sponsor.
Justification Why Any of the Above Storage Criteria Cannot Be Met	
ALL of the Following Distribution Criteria Are Met	
	* The investigator will not dispense the investigational agent to any person not authorized under the protocol to receive it. * The drug, agent, biologic may only be used in subjects under the investigators personal supervision or under the supervision of a physician who is directly responsible to the investigator. * The investigator will maintain adequate records for the receipt, storage, and disposition of the drug, including dates, quantity, and use by subjects. * The investigational agents will be stored in a secure area and in such a way to restrict access to authorized personnel only as defined in the protocol. Additionally, all associated records will be stored in a restricted area and/or locked.
Justification Why Any of the Above Distribution Criteria Cannot Be Met	

26. Financial Administration

This information will help the Financial Administration of Clinical Trials Services (FACTS) office determine whether a Medicare Coverage Analysis (MCA) is needed for the research study. If you have any questions while completing this form, please contact the FACTS office at (212) 731-7067 or FACTS@mssm.edu.

Clinical Research Study Category Investigator Initiated

Payment Options:
**** Option 1: No protocol-required services will be billed to patients or third-party payers. Does Not Need MCA***
**** Option 2: Protocol-required services (i.e., routine care services) will be billed to patients or third-party payers. Must Have MCA***
**** Option 3: Study is initiated and federally funded by a Government Sponsored Cooperative Group who will only pay for services that are solely conducted for research purposes and other protocol-required services (i.e., routine care services) will be billed to patients or third-party payers. Billing Grid Only Required, NO MCA***
**** Option 4: Study involves only data collection and has no protocol-required clinical services. Does Not Need MCA***
**** Option 5: Study is not described in any of the above options. Please describe the study and specify whether External Sponsor (i.e., industry, government, or philanthropic source) and/or patient/third party payer will pay for protocol required services. MCA MAY Be Required***

Payment Option Option 1

No MCA is needed per option selected above.

Payment Option 1:
**** Option 1A: Department/collaborating departments will act as internal sponsor paying for all protocol-required services and no protocol-required services will be billed to patients or third party payers.***
**** Option 1B: Study involves protocol-required clinical services and an External Sponsor (i.e., industry, government, or philanthropic source) will pay for all protocol-required services.***

Payment Option 1 Option 1A

27. Attachments

Type	Name	Version	Status	Filename	Uploaded Date
FDA - Package Insert for Approved Drug	Package Insert for Zomacton	1	New	ZOMACTON Somatropin Package insert.pdf	11/14/2018
FDA - Other Materials	Kolevzon IGF-1 trial performed at ISMMS	1	New	IGF-1 in PMS clinical trial.Kolevzon.pdf	11/14/2018
Consent Documents	GH consent.docx	1	New	GH Consent version date 02-26-19.docx	02/26/2019
Data Collection Sheet	DATA COLLECTION SHEET edited.docx	1	New	DATA COLLECTION SHEET edited.docx	11/15/2018
Other - Other IRB Correspondance	Research Plan PDF.pdf	1	New	Research Plan PDF 12.3.18.pdf	12/03/2018
Parental Permission Document	GH consent.docx	1	New	GH Consent version date 02-26-19.docx	02/27/2019
Data Monitoring Committee Description	Data Monitoring Committee.docx	1	New	Data Monitoring Committee.docx	11/15/2018
Package Insert Document (DRUG NAME)	ZOMACTON Somatropin Package insert.pdf	1	New	ZOMACTON Somatropin Package insert.pdf	11/15/2018
Advertisement - Website text/Screen shots/URLs	Ad for websites	1	New	Ad.docx	12/03/2018
Dosimetry Chart	DOSIMETRY.xlsx	1	New	DOSIMETRY.xlsx	01/17/2019
Other - Other IRB Correspondance	Correspondance regarding dosimetry	1	New	Radiation dosimetry correspondance.pdf	01/17/2019
FDA - FDA or Manufacturer Risk Determination	FDA IND exemption	1	New	FDA IND exemption.pdf	02/06/2019